Remarks/Arguments

Claims 1-15 and 17 are pending in the application. Claims 1-9 and 15 have been withdrawn from consideration pursuant to a lack of unity objection. Claims 10-14 and 17 are therefore under consideration. Reconsideration is requested in view of the above changes and the following remarks.

Claims 10 and 11 have been amended to clarify that the antigenic peptide fragment is not a heat shock protein-derived antigenic peptide fragment. Claim 10 has been amended to introduce the term "endogenous" to clarify that the antigenic peptide fragment is endogenous to the extracellular bacterial pathogen from which it is derived. Basis for this amendment can be derived from the specification at page 6, line 1. Further basis for the complex being comprised of an endogenous heat shock protein and an endogenous peptide fragment can be found in the description of the instant application at page 10, line 6 which refers to the complexes obtained from the stressed extracellular pathogen as "*endogenous SP preparations*".

Claim 11 has been further amended to improve the clarity of the claim by clarifying that the composition induces an immune response to the extracellular pathogenic bacteria from which the complexes are derived.

Claim 13 has been amended to correct a typographical error.

Response to Objection to Claim 13

Claim 1 has been amended, as suggested by Examiner.

Response to Objection of Specification

Page 7, line 18 has been amended to delete reference to *Trypanosoma sp.* The paragraph has also been amended to italicize genus names.

Response to Obviousness-Type Double Patenting Rejection

The provisional obviousness-type double patenting rejection is maintained against copending Application No. 10/363,454. In particular, claims 10, 12 and 17 are rejected as being unpatentable over claims 10 and 12 of the referenced application. Claim 12 of the '454

application has been cancelled. Thus, applicant will respond to the rejection as it relates to claim 10 of the '454 application.

A nonstatutory obviousness-type double patenting rejection is only appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). MPEP 804(II)(B)(1). As to the latter, obviousness-type double patenting requires rejection of an application claim only when it is not patentably distinct from the subject matter claimed in a commonly owned patent when issuance of a second patent would provide an unjustified extension of the term of the right to exclude granted by the patent. MPEP 804(II)(B)(1). Domination of the application claims by the patent claims alone is insufficient for a finding of double patenting. MPEP 804(II). When considering whether the invention defined in a claim of an application would have been an obvious variation of the invention defined in the claim of a patent, the disclosure of the patent may not be used as prior art. MPEP 804(II)(B)(1).

The analysis employed in an obviousness-type double patenting rejection parallels the guidelines for analysis of a 35 U.S.C. 103 determination. The factual inquiries set forth in *Graham v. John Deere Co.*, 148 USPQ459 (1966) that are applied for determining obviousness under 35 U.S.C. 103 must be employed when making an obviousness-type double patenting analysis. Id. The MPEP therefore mandates the following findings for supporting an obviousness-type double patenting rejection:

"(A) The differences between the inventions defined in the conflicting claims - a claim in the patent compared to a claim in the application; and

(B) The reasons why a person of ordinary skill in the art would conclude that the invention defined in the claim at issue is anticipated by, or would have been an obvious variation of, the invention defined in a claim in the patent." Id.

For the following reasons, the Examiner has not established that claims 10, 12 and 17 are *prima facie* unpatentable for obviousness-type double patenting over claim 10 of the '454 application.

Claim 10 of the present application as amended, the only independent claim rejected for double patenting, claims a composition for inducing an immune response to an extracellular pathogenic bacteria. The composition comprises an endogenous complex produced in-situ and extracted from the extracellular pathogenic bacteria. The complex is formed between an induced heat shock protein and an a non-heat shock protein-derived endogenous antigenic peptide fragment. Both the induced heat shock protein and the non-heat shock protein-derived antigenic peptide fragment are derived from the extracellular pathogenic bacteria. The production of the induced heat shock protein results from the exposure of the extracellular pathogenic bacteria to a stress-inducing heat shock stimulus. The formation of the endogenous complex between the induced heat shock protein and the non-heat shock protein derived antigenic peptide fragment is accomplished in an ATP-dependent reaction.

Applicant respectfully points out that claim 10 of the '454 application has been amended to direct the scope of the claim to a bacterial pathogen which has been genetically modified, as follows:

> "A composition for eliciting an immune response in a subject against a bacterial pathogen which is a component of said composition, said composition comprising:
> as the immunogenic determinant against which the immune response is elicited, the component bacterial pathogen in a genetically modified form such that at least one repressor gene for a heat shock protein gene in the bacterial pathogen is inactivated and said heat shock protein is constitutively expressed within said bacterial pathogen, and
> an adjuvant."

The rejection fails to set forth a prima facie case for obviousness-type double patenting. The composition of Claim 10 of the instant application recites a composition that requires a complex, the components of which are derived from an extracellular pathogenic bacteria, those components being (i) an induced heat shock protein and (ii) a non-heat shock protein-derived endogenous antigenic peptide fragment. Such a complex is not anticipated by the '454 application claim 10, which recites a composition containing a bacterial pathogen in a genetically modified form such that at least one repressor gene for a heat shock protein gene in the bacterial pathogen is inactivated and the heat shock protein is constitutively expressed within said bacterial pathogen. The '454 application claim 10 fails to describe any complex, let alone the specific complex recited by claim 10 of the instant application between (i) an induced heat shock

protein and (ii) a non-heat shock protein-derived endogenous antigenic peptide fragment. Thus, instant claim 10, and its dependent claims 12 and 17, are not anticipated by the '454 application claim 10.

Moreover, the rejection fails to establish that the invention of instant claim 10 is an obvious variant of any of '454 application claim 10. There is nothing in the latter that even remotely suggests the invention recited by instant claim 1. The '454 application claim 10 fails to recite any complex, let alone the specific complex recited by claim 10 of the instant application between (i) an induced heat shock protein and (ii) a non-heat shock protein-derived endogenous antigenic peptide fragment. Moreover, there is nothing in '454 application claim 10 that suggests the further features of the complex recited by instant claim 10, namely that the formation of the complex between the induced heat shock protein and the non-heat shock protein-derived endogenous antigenic peptide fragment is accomplished in an ATP-dependent reaction.

Claims 10, 12 and 17 of the present application are not directed to an obvious variant of '454 application claim 10. The instant claims define subject matter that is patentably distinct from the subject matter of the allegedly conflicting '454 application claim. Patenting of the instant claims would not provide an unjustified extension of the term of any exclusionary right conferred under a patent to issue from the '454 application.

Reconsideration and withdrawal of the obviousness-type double patenting rejection is respectfully requested.

Response to 35 U.S.C. 102 Rejections

Phipps et al. (1991, EMBO J., 10:1711-1722) – Rejection Under 35 U.S.C. § 102(b)

Examiner has maintained the rejection of claims 10-14 and 17 as allegedly anticipated by Phipps *et al.* ("Phipps"). Applicant respectfully submits that the claims are not anticipated by Phipps, for the following reasons.

Applicant submits that the teachings of Phipps do not disclose the subject matter of claims 10-14 and 17, as amended. In particular, Phipps does not disclose a composition comprising "*one or more endogenous complexes produced in-situ and extracted from the extracellular pathogenic bacteria between an induced heat shock protein which is derived from*

the extracellular pathogenic bacteria and a non-heat shock protein-derived endogenous antigenic peptide fragment which is also derived from the extracellular pathogenic bacteria" as recited in claim 10.

Phipps discloses an ATPase complex which is postulated by the authors to represent a novel type of chaperonin related to the members of the groEL/hsp90 family (page 1720, column 1, last paragraph). Page 1718, column 2, lines 9-10 teach that "*Thus it is possible that one of the two cross-reacting bands corresponds to groEL*".

Examiner has previously referred to two bands visible in Figure 10, lane h of Phipps, these bands being of 57 kDa and 62 kDa. If lane h of Figure 10 is taken to show two distinct bands, then if one of the shown bands is GroEL, then the second band can either be GroES, a chaperonin protein which complexes to GroEL. Alternatively, the second band could be representative of GroEL running on the gel as a doublet, this representing GroEL in a phosphorylized and non-phosphorylized state. Accordingly, the two distinct bands seen in figure 10, lane h represent heat shock proteins *only*. No further bands are shown in lane h of Figure 10. Hence, an antigenic peptide fragment is clearly not present, and therefore the requirements of claim 10 and 11 are not met as an antigenic peptide fragment which is not derived from a heat shock protein is not present.

Phipps does not show a complex between a heat shock protein and a non-heat shock protein-derived antigenic peptide fragment. In particular, the ATPase complex of Phipps forms complexes with complete proteins in order to facilitate their folding. This process is described in the reference of Rye et al. which is listed by the examiner in the Notices of References cited (Rye H. S. et al., Cell Vol. 97 325-338, April 30, 1999). Claim 10 of the instant application requires that the complex is formed between an induced heat shock protein and an antigenic peptide fragment. There is no disclosure in Phipps of the formation of a complex with an antigenic peptide fragment. Rather, the ATPase complex of Phipps is comprised of 2 complete protein sub-units, which in turn facilitate the folding of complete proteins, rather than protein fragments. Biologically, there would be no requirement for the ATPase complex of Phipps to facilitate the folding of peptide fragments.

The specific requirement of both claim 10 and claim 11 that the complexes which are formed comprise heat shock proteins and an antigenic peptide *fragment* which are endogenous to the extracellular pathogen is a central feature of the invention. The need for the heat shock protein to bind to an antigenic peptide *fragment* is fundamental to the invention, as it is this antigenic peptide fragment which is, in turn, presented to the immune system of a host to whom the complex is administered in order to confer protective immunity against the extracellular pathogen from which the complex was derived. This concept is clearly set out in the introductory portion of the instant specification, with page 1, lines 10-24, teaching that peptide fragments are presented on MHC molecules, with these antigenic peptide fragments being recognized by T cells. This results in antigen-specific T cell proliferation. In turn, page 2, lines 25-30, teach that heat shock proteins present peptide fragments to MHC molecules, such that the antigenic peptide fragments can be presented to the immune system. Accordingly, in order to contribute to the antigen processing and presentation pathway, the heat shock protein must bind only to an antigenic peptide *fragment*, such that that fragment can, in turn, be loaded onto an MHC molecule and then presented to T cells. The concept of the heat shock protein binding to protein fragments is further discussed in the instant specification at page 3, lines 1-15. The invention does not envisage a heat shock protein binding to another protein, and in fact, by defining the complex as a heat shock protein and an antigenic peptide *fragment*, the claims of the instant application specifically exclude this. Accordingly, the binding of a heat shock protein to another protein, which is not a protein fragment, does not fall within the scope of the claims of the instant application.

For these reasons, it is therefore respectfully submitted that the teachings of Phipps do not anticipate the claims of the instant application.

Wawrzynow *et al.* (1991, EMBO J., 9:1867-1877) – Rejection Under 35 U.S.C. § 102(b)

Examiner has maintained the rejection of claims 10 and 11 as allegedly anticipated by Wawrzynow *et al.* ("Wawrzynow"). Applicant respectfully submits that claims 10 and 11 are not anticipated by Wawrzynow, for the following reasons.

Examiner is incorrect in asserting that Wawrzynow teaches the complexes recited in the claims of the instant application. For example, claim 10 requires that the antigenic peptide fragment be "*a non-heat shock protein-derived endogenous antigenic peptide fragment which is also derived from the extracellular pathogenic bacteria*". Simply put, the λO protein is not derived from an extracellular pathogenic bacteria, that is, it not a peptide fragment endogenous to the extracellular pathogen, as required by claim 10, and as clarified by the amendment to that claim. Rather, the λO protein is derived from a bacteriophage, this being a virus which infects a bacteria. The features of claim 10 require a composition for "*for inducing an immune response to an extracellular pathogenic bacteria*". The immune response in Wawrzynow is induced against a bacteriophage protein, not an extracellular pathogenic bacteria. Furthermore, claim 10 requires a "*composition for inducing an immune response to an extracellular pathogenic bacteria*". This limitation of the claim cannot be met by the teachings of Wawrzynow, as the λO protein is derived from a bacteriophage and therefore, if administered to a subject, could result in an immune response being directed against the bacteriophage, rather than the extracellular pathogenic bacteria.

Likewise, claim 11 also relates to a "*composition for inducing an immune response to an extracellular pathogenic bacteria*". Again, this limitation of the claim cannot be met by the teachings of Wawrzynow as the λO protein is derived from a bacteriophage and therefore, if administered to a subject, could result in an immune response being directed against the bacteriophage, rather than the extracellular pathogenic bacteria.

Furthermore, claim 11 requires the production of endogenous heat shock protein/antigenic peptide fragment complexes. Wawrzynow simply does not teach of such a complex, as the λO peptide is *not* a fragment. Furthermore, claim 11 requires that the heat shock protein has been induced as the result of a heat shock. For the reasons stated in detail in the response to the previous office action issued on this application, the heat shock protein of Wawrzynow is not an induced heat shock protein. This difference is material. The difference between a constitutively expressed heat shock protein and an induced heat shock protein is discussed in the instant specification at page 6, line 25-31 which read "*... the treatment of extracellular pathogen organisms with stress-inducing stimuli produces SP complexes which are*

more immunogenic than ...SPs derived from uninduced organisms". Hence, induced heat shock proteins, in the sense of those recited in claim 11, are not taught by Wawrzynow.

Examiner states in the office action of September 18, 2010, that *"it is the position of the examiner that the process by which the claimed complex is produced is not as critical as long as the product is the same or equivalent product produced by a different process".* Examiner further indicates that page 1868, column 1, last line of Wawrzynow teaches that ClpX is *"under heat shock regulation".* However, virtually all heat shock proteins are under the control of heat shock regulation, as they can be with constitutively induced (during times when there is no heat stress), or induced in response to a heat shock. The claims of the instant application require that the heat shock protein is an *induced* heat shock protein. As set out in detail by the Applicant in the foregoing response, neither the Wawrzynow reference, not the paper of Wojkowiak previously submitted by the Applicant, show that the ClpX protein was induced by a heat shock. This is a fundamental point and simply cannot be swept aside and ignored by the examiner, as the difference between a constitutively expressed heat shock protein and an induced heat shock protein is significant. This difference is exemplified in the instant application in Example 3 and most particularly at page 15, lines 18 to 21, where it is taught that the profiles of the antigenic peptide fragments complexed with constitutive heat shock proteins were significantly different from those complexes to the same heat shock proteins whose production had been induced by heat shock. In this regard, further reference is made to the response filed by the Applicant to the office action of December 12, 2008 and to the associated arguments set forth in relation to the submitted reference of Mogk *et al.*, 1999 (Mogk A. *et al.* EMBO, vol. 18, No.24, pp 6934-6949).

Hence, it is entirely incorrect for Examiner to state that *"The ClpX heat shock protein-λO peptide complex of Wawrzynow et al was produced by a different process, but is the same or equivalent heat shock protein/peptide complex as now claimed... ".* Furthermore, claim 10 requires an antigenic peptide *fragment*, whereas the λO peptide disclosed in Wawrzynow is a *full length* protein, not a fragment.

Therefore, for the above reasons it is respectfully submitted that there is no disclosure in Wawrzynow which anticipates claims 10 and 11

Laminet *et al* (EMBO (1990). 9(7): 2315-2319) – Rejection Under 35 U.S.C. § 102(b)

Examiner has rejected claims 10, 11 and 13 as allegedly anticipated by Laminet *et al.* ("Laminet"). Applicant respectfully submits that claims 10 and 11 are not anticipated by Laminet, for the following reasons.

Claim 10 of the instant application is not anticipated by Laminet as Laminet does not disclose "*one or more endogenous complexes produced in-situ and extracted from the extracellular pathogenic bacteria between an induced heat shock protein which is derived from the extracellular pathogenic bacteria and a non-heat shock protein-derived endogenous antigenic peptide fragment which is also derived from the extracellular pathogenic bacteria*". In particular, Laminet discloses a complex of beta-lactamase with GroEL or a GroEL/ES complex. Accordingly, Laminet does not disclose a complex with an antigenic peptide *fragment.*

For the same reason, claim 11 is not anticipated by Laminet. Claim 11 also recites complexes formed from an antigenic peptide *fragment.*

Furthermore, Laminet teaches that Mg^{2+} ATP is present in the buffer. However, the presence of Mg^{2+} ATP in the buffer will result in the dissociation of any GroEL/beta-lactamase complex. As described in the reference of Rye et al. as cited above, although the initial hydrolysis of ATP facilitates the binding of a peptide fragment to a chaperone protein, the continued presence of the ATP would result in the dissociation of the complex. Accordingly, in the presence of Mg^{2+} ATP, any protein of Laminet will simple dissociate into its component parts (see for example, page 2318, column 1, 2nd paragraph ("the molecule is simply released after Mg^{2+} ATP addition") as well as the remarks in the last paragraph relating to "Mg^{2+} ATP driven release from GroEL/ES). The fact that ATP can be used to dissociate the peptide bound by a heat shock protein is highlighted in the instant specification at page 10, lines 20-23 which teach that "*If desired, the specific antigenic peptide fragments can be recovered from the complex, for example by treatment with ATP using conventional techniques*".

Therefore, for the above reasons it is respectfully submitted that there is no disclosure in Laminet which anticipates claims 10, 11 and 13.

Ferrero *et al* (Proc. Natl. Acad. Sci. USA) – Rejection Under 35 U.S.C. § 102(b)

Examiner has rejected claims 10-14 as allegedly being anticipated by Ferrero *et al.* ("Ferrero") in light of evidence provided by Schumann (2000). Applicant respectfully submits that claims are not anticipated by these references.

Examiner cites Ferrero at page 6499, column 2, para 2 "*The physical association between H. pylori HSP and urease*". However, urease is not an antigenic peptide *fragment* as required by the claims of the instant application, but rather a complete protein. Examiner's reliance on the citation of part of a sentence in vacuum within the greater context of the reference is tenuous, at best. There is not teaching in Ferrero as to whether the HspA protein is induced as the result of exposing the *H. pylori* to a stress-inducing heat shock stimulus. It cannot be clearly and unambiguously stated that the complexed referred to in Ferrero as "*the physical association between H. pylori HSO and urease*". Furthermore, both HspA and urease are complete proteins, while the claims of the instant application require a complex formed between a heat stress-induced heat shock protein and an endogenous antigenic peptide *fragment*. Such a complex is not taught by the reference.

Notwithstanding the fact that the B subunit of *H. pylori* urease described in Ferrero is not a fragment, the fragment would have no means to bind to GroES. Specifically, Ferrero discloses the use of a dual antigen preparation comprising *H. pylori* GroES-like protein and the B subunit of *H. pylori* urease. However, GroES is effectively the "lid" of the chaperonin cylinder which is formed by GroEL. Hence, GroES has *no role* in the binding of proteins which may be associated with the GroEL/GroES complex.

Therefore, for the above reasons it is respectfully submitted that there is no disclosure in Ferrero which anticipates claims 10-14.

Status of Application No. 10/363,454

The status of the '454 application, since the last action reported (an office action mailed Aug. 18, 2008) is as follows. Further office actions issued on June 2, 2009 and February 19, 2010, with a response to the June 2, 2009 office action filed by applicant on Dec. 4, 2009. The claims of the '454 application were rejected in the February 19, 2010 office action under Section

35 USC 112 (written description; enablement). Applicant has not yet filed a response to the office action.

Status of Application No. 10/049,702

In an Information Disclosure Statement filed June 16, 2009, applicant gave notice of applicant's copending application 10/049,702, directed to related subject matter. Substantive office actions were mailed in the '702 application on the following dates: March 27, 2004, Feb. 22, 2006, March 22, 2007, Feb. 10, 2008 and Dec. 7, 2009. Prior art asserted in rejections included US 6,048,530, WO 95/2492, and US 5,961,979, all of Srivastava *et al.*, and all of which are of record in the present application The claims of the '702 application were most recently rejected under 35 USC 112, first paragraph (written description), and under 35 USC 102 in view of Srivastava *et al.* WO 95/2492, and US 5,961,979. Applicant has not yet filed a response to the Dec. 7, 2009 office action the '702 application.

Conclusion

The claims remaining in the application are believed in condition for allowance. An early action toward that end is earnest solicited.

Respectfully submitted
CAMILO ANTHONY LEO SELWYN COLACO

BY

DANIEL A. MONACO
Reg. No. 30,480
DRINKER, BIDDLE & REATH, LLP.
One Logan Square
18th and Cherry Streets
Philadelphia, PA 19103-6996
(215) 988-3312
(215) 988-2757 – fax
Attorney for the Applicant